West Virginia University
NSG - 533

Progress Report for Space-Oriented Research

Title of Research Project:

Cardiovascular, Respiratory and Autonomic Nervous System Responses to Acute Hypoxia

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Report Covers Period: July 1, 1964 to December 31, 1964

A. Summary of Experiments and Investigations to Date

To date a total of 22 experiments have been carried out. These experiments have studied the effects of nitrous oxide on myocardial contractile force, heart-segment length, arterial blood pressure, heart rate, venous pressure, and cardiac output in dogs in order to promote a more complete understanding of the mechanisms of the cardiovascular system.

Effects of N_2O on Myocardial Contractility. Although Price and Helrich demonstrated contractile changes in the heart under N_2O anesthesia using a heart-lung preparation, no work had been pursued with the heart in situ and with intact innervation. Changes were studied using a modified Cushing myocardiograph in three dogs, in order to determine length-tension relationships. In all dogs dilatation of the ventricle resulted in an increase in segment length. After the length of this segment had been increased mechanically, the "developed tension" (systolic minus diastolic tension) was calculated. For a given length it was shown that the developed tension was less than control tension while nitrous oxide was administered. It followed then that maximum tension developed by the heart while under N_2O was less than that developed while the animal was breathing room air. Results were similar after a control period in which the animal breathed pure oxygen, confirming that contractile force was not due to changes in oxygen concentration, but was due entirely to the effect of nitrous oxide.

The remainder of the animals tested were thoracotomized and a Brodie-Walton strain gauge sutured to the right ventricle in order to monitor contractile force. After initial administration of N_2O a substantial number of the dogs

exhibited a "sympathetic burst" during which blood pressure and contractile force greatly increased, in some cases to an extent greater than control. An epidural block using lidocaine was performed to interrupt sympathetic innervation at the cervical level. This eliminated the "sympathetic burst" but did not significantly alter the depression in contractility beyond that of animals with intact sympathetic innervation.

This work bears out the concept of Wilkie that muscle functions as a two component system; comprised of a contractile component which shortens with excitation, and a series elastic component which develops tension when the contractile component shortens under conditions of isometric contraction. Under nitrous oxide it was seen that apparently there is a passive relaxation of the contractile component, with no discernible change in the elasticity of the muscle. The rate of tension developed at different imposed lengths decreased, suggesting that the rate of shortening of the contractile component was reduced.

Effects of Nitrous Oxide on Arterial Blood Pressure, Venous Pressure, Heart Rate, and Cardiac Output. In all groups it was noted that although myocardial contractile force was decreased by N_2O, arterial blood pressure, venous blood pressure, heart rate, and cardiac output remained constant and remarkably stable.

This phenomena was compatible with contractile changes when correlated with the work of Burch, et al. and Burton who suggested that force on the internal wall of the ventricle could be equated with the product of the intraventricular pressure and the surface area of the ventricle, visualizing the heart as a sphere.

Formulated, this appears as the equation: $F = fwr^2 \times P$ where: F = force in dynes; r = radius of the spherical ventricle; and P = the pressure in mm Hg.

The hoop tension of the muscle may be defined by the equation: $T = r^2 \times P$ An analysis of these formuli reveal several facts. The muscle possesses a 4 to 1 mechanical advantage over the distending force. The heart size in increased end diastolic pressure is less than that which is seen in passive relaxation. With passive relaxation during nitrous oxide administration the ventricular volume increases at a given end-diastolic pressure, resulting in a greater force on the myocardium. More tension, in the face of this increased heart size, is therefore required to raise the pressure to a given diastolic pressure.

Thus it is suggested that although nitrous oxide depresses the tension producing ability of the myocardium at a given segment length, passive relaxation increases the heart segment length resulting in a greater tension, thus maintaining normal outflow and pressure parameters.

B. Evaluation of Findings to Date

The hemodynamic changes studied in this experiment are felt to be of significance in adding to our knowledge of the cardiovascular system, which in turn, is of paramount significance in the physiological aspect of manned space flight. The information gained in these experiments is considered of importance to the field of medicine, particularly that of anesthesia.

C. A Description and Statement of Objectives of Research to be Conducted for the Balance of the Period of the Grant

Experiments are planned involving the mobilization and excretion of catecholamines during varying periods of hypoxia. Myocardial changes and contractile force will

be monitored during these periods. This department has recently been equipped with an automatic fluorometric device for the analysis of catecholamines which enables greater numbers of samples to be determined than with the manual method over a given period of time. Blood and urine catecholamine levels will be measured. Two hypobaric chambers, one small, and one large enough to be used for human physiologic experimentation are available at the Medical Center.

D. Plans for Publication of Results

A full manuscript for work reported in the period January 1, 1964 to August 30, 1964 is being prepared at this time. Material covered in this report has been completed and submitted for publication.

E. Possibilities for Expansion of Development of this Project into a Long Range Major Research Effort

In addition to the previously reported prospectus concerning myocardial and hemodynamic changes, it is felt that a comprehensive study of catecholamine uptake and excretion would be an excellent correlative factor in a long range program directed towards understanding of the cardiovascular system under conditions that might be met in manned space flight.

Facilities and Equipment Available for Carrying on Research Training. The facilities of the Department of Pharmacology are new. They are designed for maximum efficiency in carrying out research and teaching. Adequate laboratory and office space is available for conducting the program outlined in the original grant application. These facilities include polygraph equipment, a well-equipped mammalian cardiovascular laboratory, surgical equipment, pressure transducers,

special transducers for measurement of myocardial length and tesnion, Beckman Medical Gas Analyzer (Spinco Model LB-1), Chain-Compensated Gasometer, Van-Slyke Manometers, equipment for determining hematocrits, percent oxygen saturation, and other specialized equipment for cardiovascular and respiratory experiments. A new cardiovascular laboratory with fluoroscope and image intensifier equipment, Gilford Cuvette Densitometer (Model 103) for Cardio-Green dye dilution studies of cardiac output and transducers and read out systems for blood pressure measurements have been added to the Medical Center facilities. A Technicon fluorometric AutoAnalyzer has been in use for approximately six months in this department. Its value in the assay of catecholamines was mentioned in part C.

Three graduate students will receive the degree of Doctor of Philosophy as a result of work in this department in June, 1965. It is anticipated that three degrees of Master of Science will also be awarded at this date.